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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,210	03/09/2005	Evy Lundgren-Akerlund	10676.0010	4342

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,210	LUNDGREN-AKERLUND, EVY	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *5,7-14 and 16-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6, 15 and 19-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/17/08 has been entered.

2. Claims 1-22 are pending.

3. Claims 5, 7-14 and 16-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

4. Claims 1-4, 6, 15 and 19-22 are under examination as they read on a method of identifying a mammalian mesenchymal stem cell using a marker comprising an integrin alpha 10 chain expressed on the cell surface of a mesenchymal stem cell or intracellular in mesenchymal stem cell as a marker for mammalian mesenchymal stem cells, wherein the expression is detected by an immunoassay.

5. Regarding Applicant's comments on the finality of the previous Office Action, the Examiner notes that (1) the claims were amended and new claims 19-22 were added on 8/7/07, (2) Applicant's arguments are part of the amendment, filed on 8/7/07 and (3) the previous Office Action, mailed 10/17/07, does not introduce new ground of rejections as contended by Applicant, but rather the ground of the rejection has not change. The Examiner's rebut to Applicant's assertions that the invention is enabled does not constitute a new ground of rejection. The arguments were provided to counter Applicant's assertions that the claimed method is enabled. Applicant's assertions/arguments necessitate, warrant and justify the Examiner's rebuttal. Accordingly, the finality of the pervious Office Action is proper.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-4, 6 and 19-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The recitation "correlating the integrin alpha 10 chain expression detected in c) with the cell being the mesenchymal stem cell" in claims 1d and 3d is ambiguous. It is unclear whether an inverse (negative) or direct (positive) correlation exist between the integrin alpha 10 chain expression and the cell being the MSC.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-4, 6, 15 and 19-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide enablement for a method of using a marker comprising an integrin alpha 10 chain expressed on the cell surface of a mesenchymal stem cell or intracellular in a mesenchymal stem cell as a marker for mammalian mesenchymal stem cells, as claimed in claims 1-4, 6, 15 and 19-22. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The claims encompass measuring integrin chain alpha10 in samples containing a mesenchymal stem cell (MSC) as a molecular marker. However, the hMSC must express the marker recognized by the "molecule" in order for the method to work. The specification fails to demonstrate that all MSCs express the claimed marker. The specification fails to identify bone marrow-, articular cartilage- and synovium-derived cultured MSCs using the claimed alpha10 marker. It is also noted that articular chondrocytes also express alpha10 marker. It cannot be seen how the method would be used to identify MSC from articular cartilage. Further, the specification fails to demonstrate that untreated MSCs express α10 chain (control). The specification fails to show that α10 expressing MSCs (FGF-2 treated or untreated) would have multiple lineage potential to differentiate into all of the various lineages of MSC, such as osteocytes, muscle cells, myotubes, stromal cells, T/L fibroblasts, adiposcytes, tenocytes, dermal cells among other cells. The specification lacks sufficient guidance on whether the α10 positive MSCs have the potential to involve in differentiation to osteogenesis, myogenesis, marrow stroma, tendogenesis/ligamentagensis among other. It is well known in the art that each differentiation involves multiple steps controlled by growth factors and cytokines. Accordingly, the skilled in the art would doubt that the FGF-2 treated cells represent a population of mesenchymal stem cells.

The specification examined alpha10 integrin expression in FGF-2 treated culture MSCs from human bone marrow aspirates. The specification under example 3 (page 25) discloses detection of MSC expressing the integrin alpha10 from human colony-forming cells derived from human bone marrow. The Example in the specification discloses that colony-forming cells from human bone marrow express the integrin alpha 10 represent a population of mesenchymal stem cells. Further, the influence of FGF-2 on alpha l0 expression on hMSC was investigated. Cells treated with EGF-2 formed colonies typical of MSCs expressed the integrin alphal0 (see figure 4b), while the control did not. However, the control is the claimed mesenchymal stem cells, and the FGF-2 treated mesenchymal cells give a cell population with a robust chondrogenic response (giving rise to or forming cartilage) as is evidenced by Varas et al, (Stem Cells and development 16:965-978, 2007). Varas et al teach that FGF-2-treated cells had an increased mRNA expression of COL2A1 and aggrecan. Varas et al teach concluded that the results demonstrate that chondrogenicity increased with FGF2 treatment and correlated with high expression of α10 (see page 972, bridging ¶). Lundgren-AkerLund et al (abstract 2002) report that α10 and type II collagen appear after day 5 in culture a defined chondrogenic medium. Lundgren-Akerlund et al concludes that α10 integrin subunit may be useful markers for the process of chondrogenesis. Lundgren-Akerlund et al (2006) teaches that MSCs cultured under conditions that favours expression of α10, has an enhanced capacity to synthesize cartilage-specific molecules. Taken together their results strongly suggest that integrin α10 is a unique cell surface marker for chondrocytes and MSCs with chondrogenic potential (see DISCUSSION & CONCLUSIONS). It seems that Applicant has identified a subpopulation of hMSC that express α10 chain. It is clear from Applicant example whether the starting material (i.e., mesenchymal stem cells) do or do not express alpha 10 integrin on the cell surface or intracellular (see Fig. 4). Yet, Applicant is claiming a method of utilizing alphal0 integrin a marker for MSC.

The specification under Example 1 (page 22) discloses detection of integrin alpha10 (intracellular) and integrin alpha11 chain on human MSC using immunoprecipitation technique. The result shows that hMSC in culture express both integrins alphal0 and alpha11 on their surface. However expression of alpha 10 on the surface of the hMSC does not mean that it is a marker for hMSC, or alpha 10 can be use to identify hMSC. Several proteins (e.g., integrins, collagens and proteoglycans) are expressed on the surface of hMSC, that cannot be use as a marker for hMSC. It is not clear why the detection ofalphal0 integrin can be use to identify hMSC, while the other expressed proteins cannot. Furthermore, the starting material is the claimed human mesenchymal stem cells cultured MSCBM medium for four passages. However, such results only demonstrate that the hMSC express low alpha10 and high alpha11 at passage 4, but provide nothing with respect to alpha10 is a marker for MSC. Varas et al reported that integrin subunits α10 and α11 are not detectable in BM aspirate using FACS analysis. After expansion of MSCs in culture, the cells are positive for all of the collagen-binding integrin subunits, i.e., α1, α2, α10 and α11. Varas et al teach that a10 is the only integrin alpha chain expressed by MSCs that is consistently up-regulated by FGF-2. FGF2- is known to increase the proliferation rate of MSCs and its increases their chondrogenic potential (see page 968, 2nd col., last ¶; page 974, bridging ¶). Since the expression of α10 was not in total BM (sample comprising MSCS) cells directly after preparation, i.e., day 0, it cannot be seen how the skilled in the art would use α10 as a marker for MSCs.

Further, at issue is the correlating step. The claims fail to set forth a positive or negative correlation between the alpha 10 chain expression and the MSC. Varsa et al reported that α10 is upregulated during chondrocyte differentiation of MSCs which α1 and α11 were rapidly down-regulated during the 10-day aggregate culture of MSCs, whereas integrin subunit α2 expression was not affected (see abstract and page 974, last ¶). Accordingly, in order to identify MSCs, the skilled in the art need to know whether there is a positive or negative correlation between the α10 expression and the cells being MSCs.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 3/17/08, have been fully considered, but have not been found convincing.

Regarding the heterogeneity of cell population, Applicant argues the cell population tested in Example 3 and shown in Figure 4 was not a homogeneous population of MSCs, as the Office suggested. About 4% of the cells did not express integrin α10 and were therefore not identified as MSCs. Hence, the tested cell population had a certain level of heterogeneity and the use of the anti-a10 antibody allowed to distinguish the MSCs that expressed integrin α10 from other types of cells that did not express integrin α10. As discussed in the response filed on August 7, 2007, a certain level of heterogeneity is generally found in stem cell preparations due to the inherent plasticity of stem cells. In contrast to the Office's assertion, Example 3 and the data in Figure 4 therefore provide conclusive evidence that integrin α10 expression and anti-α10 antibodies are useful as a marker of MSCs in a heterogeneous cell population that "comprises a MSC" as recited in the claims.

However, the 4% of the cells that did not express integrin α10 still MSCs. This argument supports the Examiner's position that Applicant has identified a subpopulation of hMSC that express α10, wherein the FGF-2 induces the expression of in such cells. The FGF-2 non-responders do not express α10.

Applicant submits that it the Office burden to provide evidence that integrin α10 and the anti-α10 antibodies do not work as a marker according to the claims.

The Examiner would like to point to the previous Office Actions, Applicant's specification, examples and the cited references herein for evidence. Specifically, Varas et al teach that α10 expression was not detectable at early time points but increased in expression starting at day 3. The timing of the increase in expression of α10 was similar to the expression of type II collagen

in the aggregate cultures (see page 968, last ¶). TGF-β3 treatment of MSCs for 5 days had the opposite effect, lowering the integrin α10 and increasing α11 (see Fig. 3). FGF-2 treatment increased the percentage of α10-positive MSCs from 13% to 69% during the 6 days of culture, whereas the percentage of α11-positive MSCs decreased from 88% to 44% (see page 969, 2nd col.,). The results demonstrate that chondrogenicity increased with FGF-2 treatment and correlated wit high expression of α10 (see page 972, 2nd col., top ¶). The Examiner, also points to WO 2007/099337 for the teaching that a cell culture system for the expansion and differentiation of mesenchymal stem cells using FGF2 to chondrocytes. The cell culture system comprises a subpopulation of isolated MSC selected for their expression of integrin alpha 10, as well as additives promoting expansion and differentiation to chondrocytes (see abstract). Accordingly, the burden is thus placed on Applicant to point out how the teachings of the specification go beyond the evidence provided by the Examiner to establish that the α10 is a marker for MSCs in a heterogeneous cell population such as articular cartilage- and BM-derived MSCs.

Regarding the FGF-2 effects, Applicant submits that the use of FGF-2 is not required for use of the instant invention.

It is the Examiner's position that Example 3 of the instant specification uses FGF-2 to induce the expression of α10 on MSCs, but identifies no MSCs in BM, articular cartilage or synovium to establish that α10 is a marker for MSCs. Accordingly, the instant invention is not enabled for the claimed method of identifying MSCs using anti-α10 antibodies.

Regarding the expression of α10 in MSCs and other cells, Applicant submits it is known that integrin α10 has a non-ubiquitous, restrictive expression pattern in mammalian tissues. Further, Applicant submits that integrin α10 protein expression has not been detectable in many of the tissues tested, including testis, liver, spleen or brain. Applicant concludes that surface-expressed integrin α10 can be used as a marker to distinguish MSCs from all cells that do not express this integrin chain.

However, Varas et al also reported that α10 expression very low or not detectable expression levels in freshly aspired human or mouse BM (abstract). Human BM MSCs adherent in culture were 15% positive to α10 (i.e., subpopulation) (see page 968, under RESULTS). The expression of α10 was not detectable by FACS analysis in total BM cells directly after preparation, i.e., day 0 (see page 970, bridging sentence). The immunohistochemical analysis did not detect expression of α10 positive cells in the BM (see page 971, 1st col.,). Accordingly, the skilled in the art would conclude that the integrin α10 is not express in the BM MSCs and hence is not a suitable marker.

Applicant submits that a marker does not require the property of being expressed exclusively in only one particular cell type. Rather, a marker requires that its expression non-ubiquitous and sufficiently restricted to render the marker useful. Integrin α10 certainly fulfills this

requirement. Applicant concludes that the observation that integrin α10 may be expressed in a limited number of other cell types does not render it unsuitable as a marker for MSCs.

However, the MSCs must express the α10 chain in order for α10 to qualify as a marker for MSCs. Varas et al reported that the expression of α10 was not detectable by FACS analysis in total BM (comprising MSCs) cells directly after preparation, i.e., day 0 (see page 970, bridging sentence). The immunohistochemical analysis did not detect expression of α10 positive cells in the BM (see page 971, 1st col.,).

8. Claims 1-4, 6 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite "a molecule which specifically binds integrin alpha 10 chain" as part of the invention.

Applicant has disclosed only anti-α10 antibodies; therefore, the skilled artisan cannot envision all the contemplated molecule possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

May 12, 2008

/Maher M. Haddad/
Primary Examiner,
Art Unit 1644